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Ana da Cunha Fonseca

Revisão do uso das imunoglobulinas intravenosas no tratamento e abordagem de doenças infeciosas: o caminho até agora

A review of intravenous immunoglobulins use on treatment and management of infectious diseases: the road so far

março, 2017

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A review of intravenous immunoglobulins use on treatment and managment of infectious diseases: the road so far

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Faculdade de Medicina da Universidade do Porto, 16/03/2017

Assinatura conforme cartão de identificação: Ana da Cunha Fonseca

A review of Intravenous Immunoglobulins use on treatment and management of infectious diseases: the road so far

Revisão do uso das imunoglobulinas intravenosas no tratamento e abordagem de doenças infeciosas: o caminho até agora

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ABSTRACT

Intravenous immunoglobulin is a polyspecific immunoglobulin G preparation purified from plasma pools of several thousand healthy donors and its action on several components of the immune system is believed to have a modulation effect on the inflammatory process. Nowadays, it is standard as replacement therapy in primary immune deficiencies and some secondary immune deficiencies. Regarding IVIg mechanisms of action, there's a rational for its potential use on treatment and management of infectious diseases.

In this paper, were gathered several case reports, clinical trials and reviews present in the literature to date, where IVIg is used as treatment and management of different infectious diseases, and the outcomes described, discussing its potential beneficial effect.

The information collected has shown there are no official recommendations on the use of IVIg in infectious diseases but are sometimes used off-label as adjunctive therapy. Depending on the disease, there are some reports describing possible improvement on patients' outcome, whereas others report little or no change at all, with all lacking randomized, large-scale studies to support their results.

For now, it remains only as a potential adjunctive therapy, waiting for more studies to confirm its valuable effect and understand the effect of several factors regarding the preparation and the patient which influence the outcome, in order to prove its true beneficial action, counterbalancing potential risks and high costs of this therapy.

KEYWORDS: Intravenous immunoglobulins, Mechanism of action, Infectious diseases, Treatment, Management.

RESUMO

As imunoglobulinas intravenosas são uma preparação poliespecífica de imunoglobulina G, purificada de um conjunto de plasmas oriundos de milhares de dadores saudáveis e acredita-se que, devido às suas ações sobre vários componentes do sistema imune, poderá ter efeito modulatório no processo inflamatório. Nos dias de hoje, é usada como terapia de substituição padrão nas imunodeficiências primárias e em algumas secundárias. Tendo em conta os seus mecanismos de ação, existe uma base racional para o seu potencial uso no tratamento e abordagens das doenças infeciosas.

Neste trabalho, foram reunidos diversos casos clínicos, revisões e ensaios clínicos presentes na literatura até á data, onde as IVIg são usadas no tratamento e abordagem de doenças infeciosas, e os seus desfechos clínicos e potenciais efeitos benéficos são aqui descritos e discutidos.

A informação recolhida mostrou que não existem recomendações oficias para o uso de IVIg nas doenças infeciosas, mas são algumas vezes usadas *off-label* como tratamento adjuvante. Dependendo da doença, existem alguns trabalhos que descrevem uma possível melhoria no desfecho clínico dos pacientes, enquanto outros descrevem pouco ou até mesmo nenhum efeito, faltando estudos randomizados de larga escala para suportar os seus resultados em ambos os casos.

Por agora, IVIg permanece como um potencial tratamento adjuvante, aguardando por estudos que confirmem o seu valor e para perceber o efeito de diversos fatores das preparações e do paciente

que influenciam o desfecho clínico, de modo a provar a sua verdadeira ação benéfica, contrabalançando os potenciais riscos e custos do tratamento.

PALAVRAS-CHAVE: Imunoglobulinas intravenosas, Mecanismos de ação, Doenças infeciosas, Tratamento, Abordagem.

INTRODUCTION

Intravenous immunoglobulin (IVIg) is a polyspecific immunoglobulin G preparation purified from plasma pools of several thousand healthy donors. IVIg preparation primarily contains human IgG molecules, with small amounts of IgA and IgM[1]. But then, how can a preparation with components present in every individual be able to elicit immunomodulation? The answer lays on two facts: first, the broad spectrum of specificities of IVIg, which reflect the immunologic experience of thousands of donors, cannot be found in any one individual. In fact, it has been reported variations in immune antibodies (Ab) titers from batch-to-batch, inherent to all IVIg preparations, which are important to be taken into consideration[2]. Secondly, therapeutic concentrations are four times higher than the endogenous ones, allowing a new steady state to be reached and saturation of target molecules and receptors follow, which cannot be reached under physiological conditions without the IVIg infusion.

Nowadays, IVIg preparations are standard as a replacement treatment (low-dose therapy) of patients with primary immune deficiencies (PIDs) and some secondary immune deficiencies associated with hypo- and agammaglobulinemia[2], as it is believed to deliver missing immune antibodies against pathogens, allowing substitution or passive immunization against multiple bacteria and virus. Nevertheless, IVIg is increasingly being used beyond only as a substitution, but also for the treatment of a wide range of autoimmune and systemic inflammatory diseases[1, 2]. It is also licensed as a high-dose therapy for patients with idiopathic thrombocytopenia purpura, Guillain-Barré syndrome, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy, due to its anti-inflammatory actions[3].

In this paper, it will be summarized IVIg mechanisms of action and the rational for its potential use on treatment and management of infectious diseases as well as a review of its use and outcomes in different infectious diseases reported in the literature to date.

MECHANISM OF ACTION

Understanding the mechanisms by which IVIg modulates the immune system is particularly important in order to understand their possible beneficial action and to focus research on the most important characteristics. Direct neutralization of pathogenic immunoglobulins by preventing the binding of pathological antibodies to their targets is the first obvious mechanism. Nevertheless, it may be more complex than that. The immunoglobulins have two different regions: the F(ab)2 region, which contain the sites that bind to antigens and therefore recognize specific foreign molecules; and the Fc region that, by binding to a specific class of Fc receptors and other immune molecules, such as complement proteins, plays an important role in modulating immune cell activity.

IVIg and the receptors FcγRs and FcRn

Via FcγRs, a class of receptors present on a variety of immune cells, these cells recognize the Fc region of IgG, which can generate intracellular activating or inhibitory signals. There are four types of FcγRs, two of those have two subtypes each (FcγRI, FcγRII(A or B), FcγRIII(a or b) and FcγRIV). They are all activating receptors, except for FcγRIIB, which is an inhibitory receptor. The beneficial effects of high-dose IVIg therapy might be owing to the blockage and downregulation expression of activating FcγRs by monomeric IgG. This would prevent the binding of opsonized antigens, induction of effector functions, such as phagocytosis and secretion of pro-inflammatory cytokines by macrophages, degranulation of granulocytes and activation of dendritic cells (DC's) by immune complexes. On the other hand, there is also evidence pointing

out the importance of IVIg on the modulation of the inhibitory receptor FcγRIIB, where the upregulation on 'effector macrophages' leads to their inactivation[1]. It's also important to take into consideration a class of receptors crucial to IgG half-life: neonatal Fc receptors (FcRns). These receptors are expressed in the endosomal compartment of the intestinal epithelium, vascular endothelium and macrophages, and regulate serum IgG levels by binding pinocytosed IgG in the endosomes and recycling it to the cell surface, thereby rescuing it from degradation in lysosomes. High dose IVIg therapy leads to saturation of this receptor by IgG, resulting in enhanced clearance of pathogenic autoantibodies, which are replaced by IVIg's IgG coming from healthy donors[1, 3].

IVIg and inhibition of complement factors

IgG present in IVIg binds to activated C3b and C4b through its Fc portion, thus a high concentration of soluble monomeric IgG may prevent the damage of tissue by deviation of the complement cascade from the target tissue to the 'exogenous' IgG in the circulation[3, 4]. IVIg can also bind and saturate the complement receptors CR1 and CR3 in activated macrophages thus preventing the destruction of target cells already bound by pathogenic antibodies[5].

IVIg and superantigen neutralization

Superantigens can directly activate T cells by binding to the T cell receptor (TCR) through its Vβ region and at the same time by binding to the MHC class II molecules in a non-restricted mechanism. Thus, superantigens can lead to a major polyclonal response which can lead to serious clinical consequences. This response can be prevented by immunoglobulins present in IVIg (such as against TSST-1 and staphylococcal enterotoxins) which are capable of binding bacterial and viral superantigen epitopes as well as some Vβ regions on the TCR. Therefore, these anti-microbial antibodies can be considered as immunomodulatory[2, 5].

IVIg and cytokine production modulation

Physiologic autoantibodies to IL-6, IL-1, TNF-α, IL-8, GM-CSF and others have been found in healthy individuals. Consequently, IVIg contains natural anticytokine autoantibodies. It is possible that anti-inflammatory activities of IVIg are mediated by neutralizing overshooting pro-inflammatory cytokines, which may be responsible for an immediate relief of life-threatening condition associated with the rapid considerable elevation of cytokine levels[5].

IVIg and apoptosis modulation

IVIg contains natural anti-Fas receptor autoantibodies which are able to block molecular Fas ligand/Fas receptor interactions and consequently prevent apoptosis (for example, preventing keratinocyte apoptosis which is beneficial in the treatment of patients with toxic epidermal necrolysis). However, it has also been reported agonistic anti-Fas receptor antibodies in IVIg preparations, which might indicate IVIg anti-inflammatory effects also by inducing apoptosis in inflammatory cells, such as activated T cells, neutrophils or eosinophils[2].

IVIg and differential antibody glycosylation

IgG antibodies are glycoproteins that contain a sugar moiety attached to each of the asparagine 297 (N297) residues in the two chains of the antibody Fc fragment, forming part of the scaffold for FcγR binding. The importance of this sugar moiety is highlighted by the loss of therapeutic activity of deglycosylated IVIg preparations[3, 5].

IVIg and innate and adaptive immune system cells

There is quite a range of changes induced by IVIg preparations on the different types of immune cells. These changes are summarized in figure 1.

ADVERSE EFFECTS

The reason for IVIg adverse reactions is still not clear, although some studies have speculated it may be due to the antigenicity of the IgG itself, large molecular weight IgG aggregates, the presence of an antibody to a circulating microbial antigens or self-antigens, complement activation or direct release of cytokines from mononuclear cells[6]. The majority of studies to date have pointed out that beneficial effects of IVIg preparations lay on the action of monomeric IgG and that dimers and aggregates in IVIg preparations are believed to be responsible for its side effect, as multimeric IgG aggregates may activate FcRs unspecifically. Nevertheless, the evidence is emerging that IgG dimers or multimers, which are usually regarded as pro-inflammatory compounds, can also mediate suppression of immune responses, as shown in different experimental models with idiopathic thrombocytopenia purpura[7] and *Listeria monocytogenes* infection[8]. Owing to the large donor pool and different manipulations during the purification process of IVIg, complexes of anti-idiotype antibodies with complimentary idiotypes can be formed. Therefore, therapeutic IVIg preparations should contain less than 1% of aggregates and 3–15% of IgG-dimers, the reason why several precautions are taken during the production process to keep the content of multimers minimal. However, in many instances, not the IgG preparation itself but rather product stabilizers such as sugar, salt content or denatured aggregated proteins are responsible for adverse effects[1, 3].

Control of donors and precautions in the IVIg manufacturing ensure an almost zero risk of transmission of infectious pathogens, including transmission of prions[9]. With the optimization of the concentration step techniques and strict control measures, the side effects of IVIg administration are relatively mild, transitory and occur during or just after IVIg infusion. Severe adverse events are rare and more frequently occur among patients with predisposing factors (advanced age, poor hydration, hypertension or reduced renal function) associated with higher doses of IVIg. Possible adverse effects, their onset time and possible approach are present in table 1. A careful selection of patients, clinical monitoring and a strict follow-up (or exclusion) of patients with predisposing factors are paramount to reduce the incidence of negative events as well as implement more specific measures such as slow infusion (in case of high doses, up to 8 hours) and an adequate hydration before infusion, particularly in patients with impaired renal function and hypertension[6, 9]. It's also important to remember that the content, composition and characteristics of each immunoglobulin preparation may vary, as mentioned before, and could adversely affect patients in a different manner, highlighting that an appropriate selection and administration of immunoglobulins should be individualized to yield the optimal outcome and to prevent adverse reactions[10].

IVIG USE IN INFECTIOUS DISEASES

As seen, there are a lot of complex interactions between IVIg components and the different constituents of the immune system, many of them needing further studies. But can this immune system modulation be beneficial in case of infectious disease? The development of an infectious process involves the interaction between an infecting pathogen and the immune system of the host. If the immune response triggered by this interaction is inadequate, it can lead to the development of an overwhelming infection, while a vast release of the mediators can cause a systemic inflammatory response with serious consequences. Therefore, immunotherapy with IVIg preparations may have some advantages as an adjunctive agent to antimicrobial therapy, as it modulates the immune response, preventing its possible consequences if inadequate.

There are several reports in the literature about the IVIg use on infectious diseases, mainly as prophylaxis in immunosuppressed patients, and also the benefit on patients needing to receive immunosuppressant drugs, but with an infection which contraindicates them. However, here we review IVIg use on immunocompetent patients with an established infectious disease and the outcomes with its use.

IVIg use in sepsis

Sepsis is a syndrome characterized by a systemic inflammatory response to infection that leads to rapid acute organ failure and potentially rapid decline to death, highlighting the importance to have powerful treatment options. The development of sepsis results from a complex interaction between the infecting microorganism and the host response and represents the harmful consequences of dysregulated immune response. Because of its anti-inflammatory and immunomodulating effect, IVIg has been proposed as an adjuvant therapy for sepsis, as well as in patients complicated with sepsis-induced coagulopathy (due to its effect on improving hemostatic abnormalities)[11], even though the clinical studies demonstrating their efficacy and safety are relatively small.

Although the literature review suggests that polyclonal IVIg adjuvant therapy is associated with lower mortality rates, the evidence to support a routine IVIg use in the management of septic patients is inconclusive, mostly due to the large degree of heterogeneity in treatment effect between individual studies, as shown in Soares *et al*. meta-analyses[12]. This can be explained by the fact that the underlying pathophysiologic mechanisms in septic patients are highly individualized[13], and as such, individualized treatment is required. This may be achieved if trials take a number of potential confounding factors into consideration, concerning both the patient and the IVIg preparations, such as patient immunosuppression (previous or induced by sepsis) or the concentration and antimicrobial specificities of the antibodies contained in the batches of IVIg[14], currently not assessed and which could greatly affect the outcome.

In addition to the small evidence of IVIg benefit use, its limited availability and high costs must also be considered. Soares *et al.* designed a study which assessed the clinical and cost-effectiveness of IVIg in the UK National Health Service (NHS) and concluded that the existing heterogeneity between studies affected both the potential clinical and cost-effectiveness of IVIg treatment and, hence, current recommendations for its use[15]. Currently, present guidelines do not recommend the administration of IVIg in case of sepsis[16].

Regarding sepsis in neonates and infants, due to the immaturity of different organs and tissue and the need for invasive procedures (especially in preterm neonates), they are at special risk of sepsis. Initially, a study comparing control infants with infants with suspected infection, realized that after intravenous immunoglobulin treatment, the later had an increase concentration of total IgG (all subclasses) and complement component C4, and a decrease in C-reactive protein[17]. These results could confirm the rational basis for IVIg treatment in these cases. Afterward, several studies were conducted to confirm if this rational basis had, in fact, clinical effect. Some reported a reducing in early mortality rate, though with no significant effect on overall survival rate[18], outcome improvement when used as an adjunct to supportive and antibiotic therapy[19], while others reported no significant between-group difference in death rates and major disability nor significant differences in the incidence rates of subsequent sepsis episodes[20]. More recently, Ohlsson *et al.* latest systematic review concluded that routine administration of IVIg or IgM-enriched IVIg to prevent mortality in infants with suspected or proven neonatal infection is not recommended[21]. Notwithstanding, some authors still believe that passive immunotherapy is an attractive complementary strategy to fight neonatal sepsis and further studies should be designed with realistic outcomes using the immunoglobulin preparation with the best biological background[22].

IVIg use in HIV infection

Several lines of evidence suggest that increased tumor necrosis factor (TNF)-α activity also has an immunopathogenic role in HIV infection, in which its persistent activation may enhance HIV replication and may contribute to the development of immunodeficiency and to certain clinical manifestations in HIV-infected patients[23]. Thus, down-regulation of the abnormally increased TNF-α activity may be a potential therapeutic target and is thought to be achieved by IVIg administration, leading to a slower infection progression. Another action of the administration of IVIg was a temporary decrease in T cell activation and an increase in CD4+ T cell counts, suggesting that immunomodulating therapy in HIV-1 infection could indeed be effective[24].

Despite this effect on infection progression, the majority of studies conducted regarding HIV infection and IVIg use are as prophylaxis for opportunistic infection, as seen in De Simone *et al.* study where the cumulative probability of developing an opportunistic infection over the 12 months of treatment in the group with only AZT were significantly higher than in the group with AZT associated with IVIg[25]. However, concerning the treatment of HIV-infected children with serious bacterial infections little supporting evidence is seen[26]. There are also some studies suggesting a positive effect of IVIg in other HIV associated disorders, such as thrombocytopenia[27] and myelopathy[28].

IVIg use in *Influenza* infection

Complications or ultimately death arising from *influenza* infections are often associated with hyperinduction of proinflammatory cytokine production. Therefore, immunomodulatory therapies, such as IVIg, may be potential therapeutic strategies [29]. Evidence of a beneficial effect of IVIg therapy has been obtained in the 2009 H1N1 *influenza* infections, as severe infections were treated with hyperimmune IVIg (convalescent plasma fractionated from patients who recovered from the 2009 pandemic *influenza* A(H1N1)) within 5 days of symptom onset and were associated with a lower viral load and reduced mortality[30]. Other findings suggest that IVIg preparations contain antibodies that mediate antibody-dependent cellular cytotoxicity (ADCC) against heterologous *influenza* strains and may provide at least some level of protection for individuals at high risk of severe *influenza* disease[31] or even have a role as adjunctive therapy for severe and/or drug-resistant 2009 H1N1 virus and other highly antigenically drifted *influenza* strains, particularly in the immunocompromised[32].

IVIg use in Pneumonia

Pneumonia is an inflammatory condition of the lung which can be caused by bacteria, virus, fungus or even parasites. Although the lack of studies of IVIg use in these situations, we can find some reports of successful use on refractory pneumonia with extrapulmonary manifestations due to macrolide-resistant *Mycoplasma pneumoniae* infection[33], on an adult *varicella* pneumonia complicated by acute respiratory distress syndrome[34], and a possible application in necrotizing *Staphylococcus aureus* pneumonia, as antibodies against the panton-valentine leukocidin (PVL) of this bacteria responsible for pulmonary necrosis is contained in IVIg preparations[35]. Another mechanism for IVIg beneficial effect could be by improving the phagocytic activity via activation of the membrane immunoglobulin receptors of blood granulocytes and monocytes. However, these effects were not confirmed in ICU patients with nosocomial pneumonia[36]. In spite of its potential positive effect, IVIg hasn't shown results on reducing mortality in more severe case, such as in mechanically ventilated pneumonia patients with septic shock[37].

IVIg use in *Clostridium difficile* infections

There have been several case reports describing severe and resistant *Clostridium Difficile* (*C. Difficile*) colitis with vast clinical symptoms improvement and successfully treated with IVIg[38-41]. The predominant mechanism of action for IVIg is thought to be by binding and neutralization of toxin A by IgG antitoxin A antibodies present in these formulations. Although overall appearance of the benefits of using IVIg, the small sample sizes and lack of control groups on studies do not allow recommendations to be made regarding the use of immunoglobulin in *C. difficile* infection[42, 43]. Therefore, randomized trials to clarify the role of IVIg for the treatment of these infection and to evaluate the ideal dose, timing of administration and clinical characteristics of the patient population are needed.

IVIg use in *Parvovirus* (HPV) B19 infections

Symptoms caused by acute HPV-B19 infection can vary considerably from asymptomatic to severely symptomatic. Some reports describe IVIg therapy resulting in a remarkable improvement of symptoms and functional outcome in immunocompetent patients, such as on a case of severe arthritis associated with acute HPV-B19 infection[44], probably by suppression of TNF-α production in HPV-B19-infected immune cells that infiltrate the synovial tissues; on a case of HPV-B19 chronic infection with neurological impairment and arthritis[45]; on three cases of HPV-B19 infection in association with new-onset systemic necrotising vasculitis syndromes [46]; and on congenital pure red cell aplasia due to HPV-B19 infection in preterm infants[47], indicating a potentially curative role for IVIg in such disorders, due to the presence of B19 IgG neutralizing activity in these preparations[48].

There is also a series of three cases of chronic fatigue syndrome (CFS) that followed acute *parvovirus* B19 infection that, when treated with IVIg, led to clearance of *parvovirus* B19 viremia, resolution of symptoms and improvement in physical and functional ability in all patients, as well as the resolution of cytokine dysregulation[49]. However, a more recent case with similar characteristics reported symptoms persistence and also a paradoxical clinical response with increased viral replication after IVIg high-dose administration[50], suggesting a careful reconsideration for IVIg administration indication in the treatment of HPV-B19-associated CFS.

IVIg use in *Streptococcal* Infections

The major virulence mechanism of some strains of Group A beta hemolytic *Streptococcus* (GABHS) is the secretion of superantigens, such as *streptococcal* pyrogenic exotoxins (SPE)-A, SPE-B and SPE-C. Unlike traditional antigens, superantigens have the ability to stimulate immune cells without undergoing antigen processing and presentation by antigen presenting cells, and cause millions of T cells clones to be activated instead of just a few of them. The resultant excessive activation of cytokines, complement and clotting cascades, plus production of oxygen free radicals and nitric oxide, cause shock and multiorgan failure. Key roles are played by T cells and TNF, both α and β. The discovery that IVIg can reverse the hyperproliferation of T cells, neutralize superantigens and down-regulate the production of TNF is the basis for the treatment of GABHS infection manifestations, such as necrotizing fasciitis[51] and can also enhance systemic clearance of bacteria and neutrophil infiltrate into the infected tissues[52].

In invasive group A *streptococcal* infection (GAS), as in all rare diseases, large randomized clinical trials are most difficult to achieve, exemplified by Darenberg *et al.* European Randomized, Double-Blind, Placebo-Controlled Trial, which was prematurely terminated because of slow patient recruitment[53]. Therefore, there's the need to rely on comparative observational data. Taken together with the high morbidity and mortality of these infections, as well as a detailed IVIg mechanism of action, observational studies results provide evidence for IVIg as a safe adjunctive therapy that contributes to increased survival in *streptococcal* toxic

shock syndrome (STSS) and other manifestations of severe infection, and ought to be considered as treatment[54, 55]. In fact, there are several reports describing IVIg use in combination with antibiotics and surgery in cases of necrotizing fasciitis, toxic shock, and multisystem organ failure[56, 57]. Although it is difficult to assess the contribution of each part of the therapy, IVIg plus appropriate antimicrobials and surgery may be useful in the treatment of all forms of GAS infections when they are associated with STSS and also those attributable to group C and G *streptococcal* infection[58, 59]. Further prospective, randomized, clinical studies must be conducted to determine the most effective IVIg agent, timing, dose and length of therapy while taking into consideration that different preparations of IVIg may vary in their efficacy to neutralize *streptococcal* superantigens[60]. Also, highlight that patients in most of these studies and case reports were adults, and the scenario may be different in children, as seen in Shah *et al.* multicenter, retrospective cohort study, where IVIg use in children with STSS was not associated with improved outcomes but increased costs of their caring[61].

IVIg use in infection-associated hemophagocytic syndrome (IAHS)

Infection-associated hemophagocytic syndrome (IAHS) or also called reactive hemophagocytic syndrome (HS) is a form of the reactive hemophagocytic syndrome associated with viral, bacterial, fungal, mycobacterial, rickettsial and protozoal infections and with various malignant neoplasms. HS is a hyperinflammatory condition due to hyperactivation of lymphocytes and macrophages with resultant cytokine storm, leading to organ dysfunction and death. There are different pathological pathways, such as alteration of the activity of proinflammatory cytokines by binding of naturally occurring antibodies and the capacity of IVIg to alter cytokines release on a cellular level that may explain the variable therapeutic responses observed in HS associated with Dengue [62], with CMV[63], as a complication of acute hepatitis A virus infection[64] and in those with no etiologic agent identified[65]. However, due to IVIg high cost and the lack of strong evidence in such conditions, its use is limited to the most severe, life-threatening cases.

IVIg use in Acute Disseminated Encephalomyelitis (ADEM)

ADEM is an uncommon demyelinating disease of the central nervous system. It is thought to be an immune-mediated disease precipitated by various vaccinations and infectious agents. Usually no infectious agent is identified in ADEM, but it has been associated with viruses, such as *herpes simplex*, *human immunodeficiency virus*, *human herpes 6*, *measles*, *hepatitis A or B*, *varicella*, *mumps*, *influenza*, *coxsackie virus*, *epstein-barr virus* and *cytomegalovirus*, and also with bacteria, such as *Group A hemolytic Streptococcus, Campylobacter, Salmonella, Chlamydia, Mycoplasma, Legionella, Leptospira, Borrelia burgdorferi*, and *Rickettsiae*. The exact mechanism of action of IVIg in ADEM is not clear but it is thought to be more than one, such as by neutralizing the circulating antigen-antibody complexes and down-regulating pathologic cytokines production. It has been described the inclusion of IVIg in the treatment of ADEM secondary to B*orrelia burgdorferi* neuroborreliosis[66], a case report where the authors point out immunomodulation as the main responsible for the patient's improvement, as it was observed a great recovery in the neurologic status days after IVIg administration; ADEM following a hepatitis A virus infection[67], with symptoms significant improvement as a response to the treatment; and in patients with post-infectious ADEM with no etiology identified[68, 69], also exhibiting clinical improvement, with return to their previous level of functioning.

IVIg use in other infections

Diverse case reports describe the successful use of IVIg in cases of encephalitis caused by several arboviruses and also by enterovirus, such as *herpes simplex virus type I* and *Influenza A virus*[70], with symptoms and neurological examination improvement. Another article suggests

that IVIg has contributed to decreasing the number of fatal cases of neonatal *Coxsackie B viruses* infection[71], due to the high titers of antibody to enteroviruses present in such preparations. However, the amount of anti-enteroviral antibody may not be the same in each batch, so it is not guaranteed the one used on treatment contains a sufficient amount of anti-enteroviral antibody, especially if there has not been an epidemic of the specific serotype that has infected a patient in his population[72].

There's also some data indicating a possible benefit of IVIg in patients with a high probability of autoimmune disorders associated with HCV infection[73], as exogenously added Ig might modulate the immune network at various points, acting synergistically with IFNα. A case of fulminant *Human parainfluenza viruses* (HPIV)-2 myocarditis suggests clinicians should consider initiating ribavirin and IVIg in patients with HPIV myocarditis and persistent viremia not responding to supportive measures alone[74]. Also highlight a more rapid, more sustained and greater increase in platelet count with IVIg compared to placebo in cases of septic thrombocytopenia not associated with disseminated intravascular coagulation, leading the authors to recommend it in the septic patient who is bleeding or is likely to need invasive or surgical procedures[75].

CONCLUSION

Regarding IVIg known and described mechanisms of action, such as enhancing the clearance of antigens and modulation of the immune system, allied with the possible consequences of an overwhelming immune response, it presents with theoretical potential as adjunctive treatment and management of infectious diseases.

In reality, due to the lack of randomized, large-scale studies, there's no agreement in most of the results. There are no official recommendations in infectious diseases but IVIg is sometimes used off-label guided by some of the observational studies results. In most case reports present in the literature, IVIg is used as adjunctive therapy with no control group, making it difficult to surely assign the effect to one of the drugs used.

For now, it remains only as a potential adjunctive therapy, waiting for more studies to confirm its valuable effect and understand the correct dose in each case, the concerns of batch-to-batch differences and intrinsic factors of the patient, which can all influence the outcome, in order to prove its true beneficial action, counterbalancing potential risks and high costs of this therapy.

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Table 1

	Adverse effects	Onset of reaction	Comments
Mild adverse effects (common, usually immediate)	Infusion site pain, swelling, erythema Headache Myalgia, back pain, arthralgia Fever, chills, flushing Anxiety, malaise, fatigue Nausea, vomiting Hypotension, hypertension, tachycardia	Immediate reaction	Usually, resolve within the first few hours by stopping or reducing the infusion rate. May be relieved by standard anti-inflammatory drugs and less commonly with corticosteroids. It may be necessary promethazine for nausea and vomiting, and narcotics for severe pain.
	Hyponatremia Neutropenia Direct Coombs' positivity	Delayed reaction	
Moderate adverse effects (less common, usually delayed)	Persistent headache Aseptic meningitis Hemolytic anemia Serum sickness/arthritis Dermatologic complications	Delayed reaction	It can be helpful antimigraine medications for prolonged headache.
	Interference with vaccine effectiveness and/or immunodiagnosis	Late reaction	
Severe adverse effects	Anaphylactic/anaphylactoid reaction	Immediate reaction	Acute renal failure is associated with preparations containing sucrose. Acute cardiovascular events (stroke, acute myocardial infarction, thrombosis) are favored by the increased viscosity of the blood caused by IVIg (rare but clinically relevant).
	Renal complications Pulmonary complications Thrombosis/embolism Colitis	Delayed reaction	
	Blood borne Infectious diseases	Late reaction	

Figure 1

B-cell downregulation leading to decreased antibody production by:

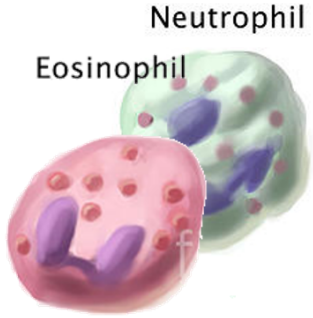
- IgG Fc region bounding to FcγRIIB in the membrane of B-cells, activating an inhibitory pathway
- and neutralization of cytokines such as BAFF (B-cell Activating Factor of the tumor necrosis factor Family) and APRIL (A Proliferation Inducing Ligand).

Modulation of Natural killer (NK) cell activity by:

- Promoting the interaction between NK cells and DCs, leading to the reduction of the antigen-presenting pool
- Induction of changes in NK cells trafficking from blood to tissue

Inhibition of T-cells proliferation and cytokine production by:

- Natural auto-antibodies against TCR, CD4 and MHC class I present in IVIg preparations
- Inhibition of IL-2 production by T-cells at a post-transcriptional level, and induction of lymphocyte apoptosis via Fas (CD95) and activation of caspases
- Expansion and activation of FoxP3+ regulatory T cells (Tregs)

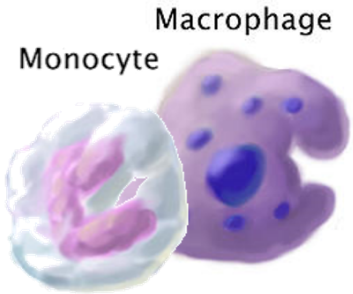


Neutrophils and Eosinophils regulation by:

- Blockage of FcγR's on their surface abrogating their activity
- Blockage of their activation (leading to cell death) by antibodies against the sialic-acid-binding Ig like lectin (siglec)-8 and siglec-9 present on the surface of these cells

Suppression of Monocytes and Macrophages activation by:

- Altering transcription of various inflammatory genes
- Lowering circulating levels of monocyte and macrophage inflammatory cytokines, tumor necrosis factor (TNF)-α and IL-1β
- upregulation of inhibitory FcγRIIB and down regulation of FcγRIII



Decrease of dendritic cells (DCs) function by:

- Inhibition of their differentiation and maturation due to the down regulation of HLA molecules and co-stimulatory CD80/CD86 molecules
- Suppression of DC-mediated activation and proliferation of auto- and allo-reactive T cells
- Suppression of the ability to uptake potential auto-antigens such as nucleosomes
- Abrogation of the capacity to secrete pro-inflammatory cytokine IL-12 upon activation
- Increasing of anti-inflammatory cytokine IL-10 production

Table 1: IVIg adverse systemic reaction, which can be: **immediate** (60% of reactions) occurring during or within 6 hours of the infusion; **delayed** (40% of reactions) occurring 6 hours to 1 week after an infusion; or **late** (<1%) occurring greater than 1 week after or even weeks or months after an infusion.

Figure 1: IVIg induced changes on the different types of immune cells.

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Nota final - Para um mais completo esclarecimento sobre este assunto aconselha-se a leitura dos requisitos do International Commitee of MedicalJournal Editors, resumidos nos números 4 e 5 do Boletim da S.P.P.R. epublicados na integra no N Eng J Med 1991; 324:424-428.

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